ASSESSMENT OF THE REPRODUCTIVE TOXICITY OF CADMIUM ON TESTICULAR FUNCTION IN MICE

Mourad TAHERTI [1,a], Imane HADJ ABEDALLAH[1], Mohammed SEHNINE[1], Nora MIMOUNE [2,3,4,b*]

[1]Laboratory of Natural Bio-Resources, Department of Biology, Faculty of Nature and Life Sciences, University Hassiba Benbouali of Chlef, PO Box 151, (02000) Chlef, Algeria.

[2] Higher National Veterinary School of Algiers, Algeria

[3]Animal Biotechnologies Research Laboratory (LBA),Institute of Veterinary Medicine (ISV), Saad Dahleb Blida University 1, Blida, Algeria

[4]Biotechnologies Platform for Animal Medicine and Reproduction (BIOMERA), Saad Dahleb Blida University 1, Algeria

ORCIDs: [a]0000-0002-9111-3750; [b]0000- 0002-0900-3908

[(*)] Corresponding author E-mail:nora.mimoune@gmail.com

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ABSTRACT

Cadmium is a heavy metal known for its toxic effects on various organs, particularly the reproductive system. The present study was conducted to evaluate the effects of cadmium exposure on the reproductive function of adult male mice. The animals were divided into two groups, a control group and a group exposed to cadmium chloride at a dose of 10 mg/L in the drinking water. Body and testicular weights, sperm vitality, testicle histopathologyand morphometry were examined to evaluate the toxic impact of this metal. Our data showed a significant decrease in body weight and, in particular, in the absolute and relative testicular weight associated with testicular atrophy. Likewise, the measured tissue metrics presented a highly significant decrease in the tubular differentiation index and the spermiogenesis index, confirming an impairment of spermatogenesis. Moreover, histological examination of the testes of the intoxicated mice revealed degeneration of the germinal epithelium, atrophy of the seminiferous tubules, enlargement of the interstitial space, vascular congestion. In addition, the analysis of sperm viability, assessed by eosin staining, showed a marked decrease of this parameter in intoxicated mice, reflecting a decline in gamete quality. In conclusion, fertility tests demonstrated a reduction in male reproductive performance. Altogether, results highlight the severity of cadmium induced testicular toxicity and reinforce its classification as an endocrine and reproductive disruptor.

Keywords: Cadmium, testicle, spermatozoa, histology, mice, fertility

Introduction

In recent years, heavy metal contamination has emerged as one of the most serious environmental problems (WHO, 2020). Their concentrations vary depending on the molecule and are ubiquitous throughout the environment (Abderrahmane *et al*., 2021). Human activities have greatly increased the spread of various substances into the environment, some of which are toxic not only to flora and fauna, but also to humans even at low doses (Chapman, 2018; Blanchard, 2020). Heavy metals such as lead, cadmium, copper, zinc, and mercury are not biodegradable, allowing them to persist in the environment for an extended period. Moreover, they are frequently introduced into the soil through various activities, particularly agricultural practices involving the use of sewage sludge, as well as metallurgical activities (Huynch, 2009). Cadmium, a white, soft, and ductile metal generally classified as a heavy and toxic transition metal, is a major environmental concern due to its particularly harmful effects (Chapman, 2018). It also poses a significant risk to human health. Daily exposure through food, water, and inhalation (smoking and occupational exposure) results in continuous human contact with this metal. Consequently, inhalation and ingestion represent the two main ways by which the cadmium enters the body. However, for the general population, food remains the primary source of cadmium exposure (Amandine, 2011). The major toxic effect of cadmium is the induction of oxidative stress. This disrupts the structure and function of the male reproductive system by affecting the blood-testis barrier and altering the development of germ cells, Leydig and Sertoli cells, ultimately leading to infertility (Ilieva and Sainova, 2022).

This study aimed to investigate the effects of chronic cadmium exposure on testicular structure and function in mice. Particularly, we investigated the histopathological alterations in testicular tissue and the impact of cadmium on sperm quality and on testicular morphometric parameters, including the tubular differentiation index (TDI) and spermatogenesis index (SPI). Accordingly, this research seeks to deepen our understanding of the mechanisms underlying cadmium-induced testicular toxicity and to assess its potentialimpact on male fertility.

Materials and Methods

Animals

The study was conducted in the animal facility and laboratories of the Biology Department, Hassiba Ben Bouali University of Chlef, Algeria. Adult male NMRI (non-inbred) mice, aged 3 months and weighing 30-35 g, were used. The animals were housed in plastic cages under standard conditions: ambient temperature of 22 ± 2°C, controlled humidity, and a 12H light/ 12H dark cycle. The mice had free access to drinking water and a standard diet (corn-based pellets). A two-week acclimatization period was allowed prior to the start of the experiment.

Experimental protocol

Animal repartition

The mice were divided into two groups: Group 1 (Control): 10 mice receiving only uncontaminated drinking water. Group 2 (Cadmium-treated): 10 mice receiving a cadmium chloride (CdCl2) solution at 10 mg/L, prepared by dissolving 10 mg of CdCl2 in 1 liter of distilled water. The solution was provided daily in 250 mL drinking bottles.

Each mouse was identified by coloring its tail using three colors (black, green, red) applied according to a coded system (1 to 3).

Body and Testicular Weight

The body weight was recorded weekly for both groups over a six-week period. Testicular weight was measured after sacrifice. The relative testicular weight was calculated using the following formula:

Relative organ weight = (Organ weight / Body weight of the mice x 100

Water and food consumption

Daily water and food intake were recorded for the second group to estimate the dose of CdCl2 consumption throughout the exposure period (Table 1).

Table 1: Water and food consumption

Week	Water consumption (mL)	Pellet consumption (g)
1	162.86	45.71
2	138.43	62.86
3	142.86	70.00
4	168.57	70.00
5	174.71	54.29
6	164.29	52.86

Fertility assessment (mating test)

A fertility test was conducted at the end of cadmium exposure (day 45) to evaluate the sexual behavior of male mice. Each male was placed in a cage with three adult, untreated females in estrus for a 10-minute observation period. Interactions between the male and females were monitored to assess sexual behavior. The following parameters were recorded: Attempts at mating, successful mating (assessed by behavioral indicators or prolonged mounting) and success criterion: the exhibition of clear copulatory behavior within the 10-minute observation period.

Sacrifice and sampling

At the end of the six-week experiment, animals were anesthetized using chloroform applied to cotton in a small airtight cage. After respiratory arrest, the testicles were removed, rinsed with 0.9% saline solution, weighed, and fixed in 10% buffered formalin for histological analysis.

Sperm parameters analysis

After sacrifice, sperm viability was assessed. The epididymis was excised and minced in a pre-sterilized physiological solution. The spermatozoa were released by diffusion, and the suspension was examined under a microscope at 400x magnification following staining. Sperm viability was analyzed using the eosin-negrosin staining method: unstained spermatozoa were considered viable, whereas those that absorbed the dye were considered as dead. The percentage of live spermatozoa was calculated based on at least 100 cells per sample.

Histological study

Immediately after removal, the testes were rinsed with 0.9% NaCl and fixed in 10% buffered formalin. This process inactivates mitotic and enzymatic activity, preventing tissue autolysis and preserving the tissue close to its physiological state. Subsequently, standard histological procedures were performed including dehydration, infiltration, embedding, sectioning, spreading, staining, and mounting of slides.The latter were observed using an optical microscope connected to a digital color camera (Optika Vision Lite 2.1).

Histomorphometry of testicular parameters

The histomorphometric analysis of the testes from control and cadmium-treated mice was performed using IC Measure software for image analysis. Over 50 histological sections per group were examined under an optical microscope(x400 magnification). The tubular differentiation index (TDI) was calculated as the percentage of seminiferous tubules containing more than three layers of differentiated germ cells derived from type A spermatogonia. The spermatogenesis index (SPI) was determined as the ratio of the number of seminiferous tubules containing spermatozoa (SPI-positive) to the number of empty tubules (SPI-negative) (Lafuente *et al*., 2020).

Ethical Statement

All the animal studies were conducted with the utmost regard for animal welfare, and all animal rights issues were appropriately observed. The animals were placed in the right experimental conditions. All the experiments were carried out according to the guidelines of the Institutional Animal Care Committee of the Algerian Higher Education and Scientific Research (Agreement Number 45/DGLPAG/DVA.SDA. 14).

Statistical analysis

Statistical analysis was performed using tukey's test for intergroup comparaison, using Past 3 software. Data for body weight and absolute and relative testicular weights were expressed as mean ± standard deviation. Differences were considered statistically significant at $P<0.05$.

Results and Discussion

Macroscopic observations

Several clinical manifestations were observed as a result of the experiment, particularly in the cadmium-exposed group. During the study, animals in this group exhibited partial hair loss and increased aggressive behavior (Figure 1). These signs indicatethe physiological stress caused by exposure to a toxic component. In contrast, control animals maintained normal behavior, regular physical activity, and smooth coat throughout the experiment.

Changes in body weight and relative testicular weight

The body weight of the experimental animals was recorded weekly throughout the study period (Figure 2). Growth curves revealed significant differences between the groups (Table 2). In the control group, a gradual increase in body weight

Figure 1: Partial hair loss in mice exposed to cadmium

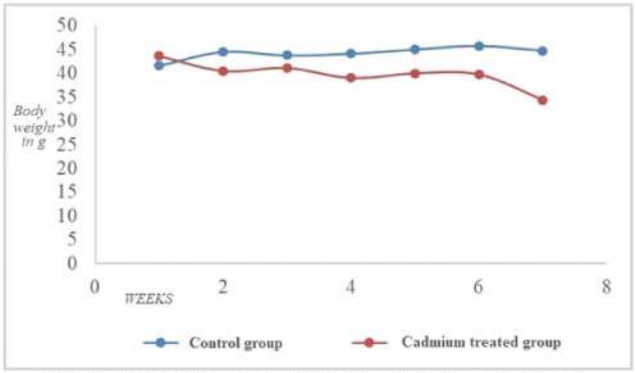

Figure 2: Evolution of body weight during the experiment

was observed, reflecting normal physiological development. In contrast, cadmium-exposed mice failed to gain weight. By the second week, body weight had declined. These findings indicate that cadmium exerts toxicity not only as a local irritant but also in systemically, negatively affecting metabolism.

Analysis of body weight changes revealed a clear difference between the two groups (Table 2). At the end of the experiment, the average body weight of the control group was 44.85 ± 2.34 g, indicating normal growth throughout the study. In contrast, the cadmium-exposed mice had a significantly lower final body weight of 39.28 ± 4.68 g (*p < 0.05). Although this variation is moderate, it indicates that cadmium adversely affected general health and physical development, potentially by reducing appetite or interfering with metabolic processes. The effects of cadmium on the testes were even more pronounced. The absolute testicular weight was significantly reduced in cadmium-exposed mice(0.10 ± 0.01 g) compared to 0.35 ± 0.05 g in control mice (p < 0.001). Similarly, relative weight of the same organ in the control group increased almost threefold compared to that of the exposed group (0.78 ± 0.12% vs. 0.26 ± 0.06%) (p < 0.001).This may indicate severe testicular atrophy in cadmium-treated mice. These findings suggest that cadmium exposure not only impairs general growth but also causes major lesions in the male reproductive system.

Table 2: Final body weight and absolute and relative testicular weight

Groups	Body weight (g)	Absolute testicular weight (g)	Relative testicular weight (g)
Control	44.85 ± 2.34	0.35 ±0.05	0.78 ± 0.12
Cd-exposed	39.28 ± 4.68*	0.10 ± 0.01***	0.26 ± 0.06***

* p<0.05, **p<0.01, ***p<0.001

Water consumption and cadmium intake

Water consumption was recorded daily throughout the experimental period to estimate the cadmium intake. On average, mice consumed 20 mL of water per day. Giving the solution concentration of 10 mg of CdCl2/L, the daily intake of CdCl2 was 0.2 mg/mouse. After conversion (mg/kg), the daily dose of cadmium consumed by a mouse weighing 35 to 40 g was identified as 5 mg/kg/day. This represents moderate, long-term exposure, simulating prolonged environmental exposure. Over the course of the experiment, the total CdCl2 intake per mouse was approximately 9 mg, based on the average daily water consumption and the 45-day duration of exposure, based on water consumption and the duration of exposure. This amount was sufficient to allow assessment of various physiological and reproductive parameters in the mice.

Sperm parameter results

Analysis revealed a pronounced reduction in spermatozoa vitality in cadmium-treated mice. The percentage of viable sperm was 15% in the cadmium-treated group compared to 63.2% in the control group (Table 3). This significant decrease indicates that cadmium markedly impairs sperm viability, reflecting its deleterious effect on germ cell integrity and, consequently, on sperm quality and potentially on fertility.

Table 3: Percentage of sperm vitality in mice from the two groups

Group	Live sperm	Dead sperm	Total observed	Vitality
Control	79	46	125	63.2 %
Cd treated	15	85	100	15 %***

***p<0.001

Histological results

Hematoxylin-eosin staining of the testis revealedclear histological difference between the 2 groups. In the control mice, the overall testicular architecture was well preserved. The seminiferous tubules (ST) displayed normal density, a regular circular arrangement, and a well-developed structure, with a thick germinal epithelium. The different germ cell types were clearly identifiable: spermatogonia (Sg) at the periphery of the tubules, spermatocytes (Sc) and spermatids (Sp) were the most abundant, and the tubular lumen is filled with mature spermatozoa (SZ). The interstitial tissue (IT) showed no signs of vascular congestion and the Leydig cells (L) were well differentiated, indicating normal testicular function (Figure 3).

In contrast, histological examination of the testesfrom cadmium-exposed micerevealed severe tissue alterations (Figure 4). A marked degeneration of the germinal epithelium was observed, characterized by a loss of organization of the different cellular layers. This disorganized cellular polymorphism indicates direct damage to germ cells and Sertoli cells induced by cadmium, likely mediated through oxidative stress and apoptotic pathways. The tubules exhibited pronounced atrophy, appearing narrow, irregular, and in some cases collapsed, reflecting a loss of maturing germ cells and inhibition of the sperm spermatogenic activity. Another notable featurewas the detachment of spermatogonia from the basement membrane, suggesting disruption of intercellular junctions essential for normal Sertoli cell function. This alteration compromises tissue stability and functionality and may initiate necrotic processes. Marked congestion of the microvasculature, accompanied by thickening of vessel walls,

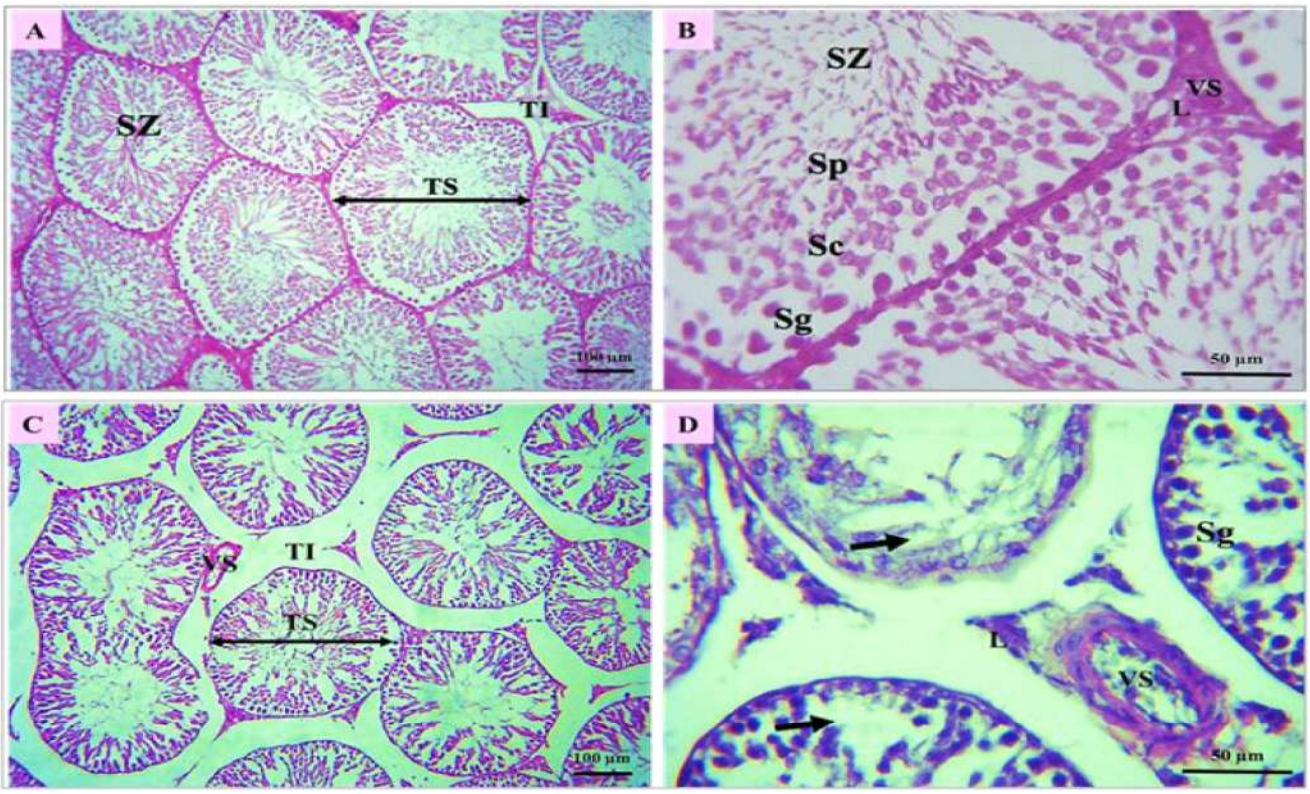

Figure 4: Histological sections of the testis in the control group (A and B) and in the cadmium-exposed group (C and D)
Sg: spermatogonia, SC: spermatocyte, SZ: spermatozoa, SP: spermatid, TI: interstitial tissue, TS: seminiferous tubule, L: Leydig cell, VS: blood vessels, ST: seminiferous tubule, BV: blood vessels, Black arrow: Detachment of spermatogonia from the basement membrane of the tubules

indicating a local or chronic inflammatory response. Such vascular alterations exacerbate tissue hypoxia, further aggravating primary and secondary tissue damage. In addition, a significant enlargement of the interstitial space between the tubules, indicating a loosening of the testicular architecture, a reaction to edema. Finally, the lumina of the seminiferous tubules contained few spermatozoa, and in some sections were completely devoid of sperm. These findings demonstrate a severe impairment of spermiogenisis indicating a profound disruption of sperm production. Collectively, these histological changes clearly demonstrate the highly deleterious effects of cadmium on testicular tissue.

Morphometric results

A histomorphometricanalysis of the stained testicular circle sections was performed using IC software for image analysisand measurement. This analysis aimed to evaluate the effect of cadmium on the morphology of seminiferous tubule cells. The following parameters were assessed: the tubule differentiation index (TDI) and the spermiogenesis index (SPI) (Figure 5).

For the control group, TDI and SPI values were high, reflecting normal spermatogenic activity. Most seminiferous tubules exhibited three or more layers of differentiated germ cells and their lumina were filled with numerous spermatozoa indicating complete spermiogenesis. In contrast, both values were highly significantly reduced in cadmium-treated animals (***P < 0.001) compared to the control group (Figure 5). TDI showed that many seminiferous tubules contained only a small cell layer, often a single layer. The SPI was also significantly reduced, reflecting a highly significant deficit in tubules containing mature spermatozoa. These quantitative findings are consistent with the histological observations and further confirm the deleterious effects of cadmium on spermatogenic differentiation and sperm production.

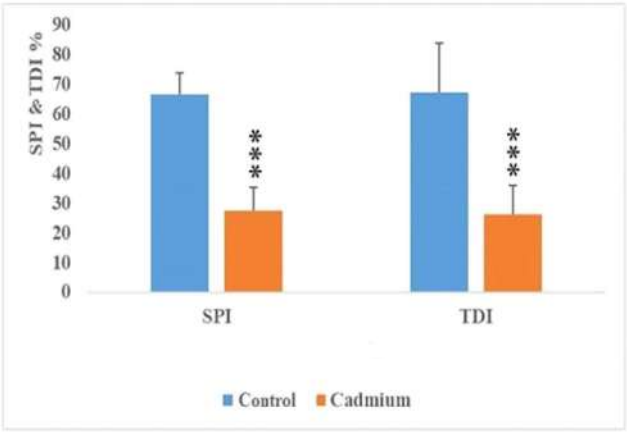

Figure 5: Tubular differentiation index (TDI) and spermatogenesis index (SPI) in the different groups (*** p < 0.001 compared with the control group)

Fertility test results

A fertility test was conducted at the end of the exposure period to evaluate the effects of cadmium on the reproductive behavior of male mice. Sexual behaviors, including approach, mounting attempts, and prolonged mounting, were assessed. All males in the control group exhibited normal sexual behavior (Table 4). In contrast, only 2 out of 10 males in the cadmium-exposed group displayed mating behavior, representing a highly significant reduction compared with controls (***P < 0.001). These findings indicate a marked decrease in libido and reproductive performance in cadmium-treated mice. This impairment is likely associated with the histologically observed damage of the testicular tissue.

Table 4: Fertility test results for both groups at the end of the experiment

Group	Number of males tested	Males that mated	Success rate (%)
Control	10	10	100 %
Cd treated	10	2	20 %***

***p<0.001

The results of this study demonstrated that cadmium exposure induces significant physiological, morphological, histological, and functional impairments of testicular function. Mice exposed to cadmium exhibited several clinical manifestations indicative of physiological distress, including partial fur loss, increased aggression, reduced feeding, and decreased activity during the first weeks of exposure. These symptoms clearly reflect the systemic toxicity of cadmium (Thompson and Bannigan, 2008; Liu *et al*., 2009). Cadmium acts as a multi-target toxicant, interfering with metabolic, hormonal, and cellular functions. Hair loss and lethargy observed in exposed mice are likely associated with severe oxidative stress induced by cadmium. Indeed, Elbetieha *et al*. (2011) and Waisberg *et al*. (2013) reported that cadmium exposure enhances free radical formation, affecting cell membranes, proteins, and DNA, thereby causing generalized cellular dysfunction. The increased aggression observed in cadmium-treated mice may also result from neuroendocrine disruption. Studies by Flora *et al*. (2016), Telisman *et al*. (2017) and Jitender et al. (2024) have described cadmium-induced neurotoxicity, including effects on multiple organs and neurological structures, particularly the hypothalamic-pituitary-gonadal axis. Such disruption could underlie the observed neurobiological changes, including alterations in social and sexual behavior in exposed mice. Finally, the preservation of normal behavior and coat condition in the control group suggests that experimental conditions were appropriate and confirms that the observed alterations are attributable to cadmium exposure.

In addition, a difference was observed between the treated and control groups in terms of absolute and relative testicular weight. Although the tests were directly affected, as evidenced by the significant decrease in relative testicular weight in cadmium-exposed animals, a significant reduction in final body weight was also noted in the treated group (39.28 ± 4.68 g) compared to the controls (44.85± 2.34 g) ($p < 0.05$). This decrease in body weight aligns with the observed reduction in food and water consumption, reflecting systemic toxicity and metabolic stress induced by cadmium. Repeated cadmium exposure has been reported to interfere with general metabolism and reduce appetite, leading to compromised body weight gain. Thus, the relative weight of the tests (testis weight normalized to body weight) was significantly reduced in exposed animals, confirming severe testicular atrophy. These findings are consistent with previous reports by Siu *et al*. (2009), Fernandez (2013), and Newairy (2017), who similarly documented reduced testicular weight in cadmium-exposed mice, associated with germ cell loss and degeneration of seminiferous tubules.

Histological analysis of testicular tissue revealed severe alterations in mice exposed to cadmium, in contrast to the well-organized architecture observed in controls. The seminiferous tubules were atrophic, cells were disorganized, and the germinal epithelium was degenerated, and the tissue exhibited marked vascular congestion, indicative of an acute inflammatory response. Similar findings have been reported by Silvina *et al*. (2014), Bhardwaj *et al*. (2021), and Candelaria *et al*. (2024), who demonstrated that acute cadmium exposure disrupts the blood-testis barrier and leads to complete uncoiling of the seminiferous tubules. Yang *et al*. (2024) further highlighted cadmium's effects on intercellular junctions between Sertoli cells and germ cells, linking this disruption to epithelial collapse that impedes normal sperm development. The vascular congestion observed in the present study aligns with local inflammatory responses, consistent with previous reports suggesting acute processes mediated by cadmium (Waisberg *et al*., 2013; Wang *et al*., 2017; Marin *et al*., 2025). These authors concluded that cadmium toxicity involves oxidative stress and the release of inflammatory mediators, predominantly activated cytokines. Epithelial alterations, manifested as enlarged interstitial spaces, are associated with early spermatogenesis impairment, reflecting direct damage to Sertoli cells. Since Sertoli cells are essential for supporting spermatogenesis, functional deficits in these cells, as observed in our study, are expected. This damage compromises the integrity of cell junctions and the blood-testis barrier (BTB), a mechanism previously described by Cheng and Mruk (2012). Overall, the histological findings confirm that cadmium exposure induces multifactorial disruption of the testicular environment, encompassing structural, inflammatory, and oxidative effects. These alterations account for the observed suppression of spermatogenesis and the significant decline in fertility, underscoring the potent reproductive toxicity of cadmium in male mice.

Morphometric analysis revealed that mice exposed to cadmium exhibited significantly lower tubular differentiation index (TDI) and spermiogenesis index (SPI) values compared to unexposed animals. High TDI and SPI values indicate active and complete spermatogenesis, whereas low values reflect impaired germ cell differentiation and reduced production of mature spermatozoa. These findings are consistent with Massanyi *et al*. (2020) and AitBenbella *et al*. (2025), who reported significant decreases in these morphometric indices following cadmium administration, attributing the changes to tubular degeneration and cellular depletion. Furthermore, Jurczuk *et al*. (2014) and Ren *et al*. (2019) demonstrated that cadmium's effects on spermatogenesis are mediated by excessive production of free radicals, which trigger lipid peroxidation of cell membranes, apoptosis of germ cells, and a reduction in the number of seminiferous tubules containing

mature spermatozoa. The observed reduction in TDI and SPI indicates that cadmium exposure inhibits cell differentiation and sperm production, reflecting a profound disruption of spermatogenesis. This morphometric impairment, corroborated by histo-anatomical defects, provides further confirmation of the decreased fertility observed in cadmium-exposed mice.

Furthermore, the mating test revealed that all control mice mated successfully, whereas only 2 of the 10 males in the cadmium-exposed group exhibited sexual behavior. This result indicates a marked reduction in libido and sexual activity, likely associated with hormonal alterations or damage to hypothalamic centers involved in reproductive behavior, as reported by Sanatiago *et al*. (2025).

Conclusions

At the end of this study, the toxicological impact of cadmium on testicular function in adult male NMRI mice was confirmed. The results obtained after six weeks of exposure demonstrated that this heavy metal significantly affects various biological, behavioral, and histological parameters. Chronic exposure to cadmium via drinking water led to a gradual alteration in weight gain, accompanied by notable weight fluctuations. Similarly, food and water intake slightly decreased in cadmium-exposed animals, reflecting metabolic discomfort and a disturbance in overall health. From a reproductive perspective, sexual behavior and mating performance declined, accompanied by a sharp reduction in mating episodes and a lower success rate in exposed males. These effects were accompanied by severe histological disorganization in the testes, characterized by atrophy and atony of the seminiferous tubules. Together, these findings confirm the toxic effect of cadmium on gonadal structure, likely mediated by oxidative stress, hormonal disruption, and breakdown of the blood-testis barrier. This study highlights the importance of limiting environmental exposure to this endocrine disruptor.

Conflict of interest

The authors declare that they have no competing financial interests or personal relationships that could have appeared to influence the work reported in this paper

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